MODE OF ACTION.

1. **Inhibitors of cell wall synthesis.** While the cells of humans and animals do not have cell walls, this structure is critical for the life and survival of bacterial species. A drug that targets cell walls can therefore selectively kill or inhibit bacterial organisms. Examples: penicillins, cephalosporins, bacitracin and vancomycin.

2. **Inhibitors of cell membrane function.** Cell membranes are important barriers that segregate and regulate the intra- and extracellular flow of substances. A disruption or damage to this structure could result in leakage of important solutes essential for the cell’s survival. Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorly selective and can often be toxic for systemic use in the mammalian host. Most clinical usage is therefore limited to topical applications. Examples: polymyxin B and colistin.

3. **Inhibitors of protein synthesis.** Enzymes and cellular structures are primarily made of proteins. Protein synthesis is an essential process necessary for the multiplication and survival of all bacterial cells. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria, and consequently leads to the death of the organism or the inhibition of its growth and multiplication. Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, tetracyclines.

4. **Inhibitors of nucleic acid synthesis.** DNA and RNA are keys to the replication of all living forms, including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: quinolones, metronidazole, and rifampin.

5. **Inhibitors of other metabolic processes.** Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. Sulfonamides target and bind to dihydropteroate synthase, trimethoprim inhibit dihydrofolate reductase; both of these enzymes are essential for the production of folic acid, a vitamin synthesized by bacteria, but not humans.

DRUG RESISTANCE.

Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth. Some organisms are inherently resistant to an antibiotic. For example, most gram-negative organisms are inherently resistant to *vancomycin.*
- **Depot forms:** Procaine penicillin G and benzathine penicillin G are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

2. **Absorption:** Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora. Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid. Therefore, they should be taken on an empty stomach.

3. **Distribution:** The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed. Penicillin levels in the prostate are insufficient to be effective against infections.

4. **Metabolism:** Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of penicillin G may occur in patients with impaired renal function.

5. **Excretion:** The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Nafcillin and oxacillin are exceptions to the rule. They are primarily metabolized in the liver and do not require dose adjustment for renal insufficiency. Probenecid inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The penicillins are also excreted in breast milk.

**Adverse reactions.**
Penicillins are among the safest drugs, and blood levels are not monitored. However, adverse reactions may occur.
1. **Hypersensitivity:** Approximately 5% percent of patients have some kind of reaction, ranging from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the β-lactam antibiotics. To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

2. **Diarrhea:** Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. Pseudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.

3. **Nephritis:** Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis.

4. **Neurotoxicity:** The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. **Hematologic toxicities:** Decreased coagulation may be observed with high doses of *piperacillin*, *ticarcillin*, and *nafcillin*.

**Natural Penicillins.**

Benzy1 Penicillin - (Penicillin G) — one of the natural penicillins used clinically and unstable in water solution, gastric juice at pH 2.

**Antibacterial actions.**

Spectrum includes:

- Gram positive cocci - *S. Pyogenes*, non β-lactamase producing *S.aureus*, sensitive *S.pneumoniae* and aerobic gram positive cocci.
- Gram positive bacilli - *C. diphtheriae*, *B.anthracis*, anaerobic *C.tetani*, *C.perfringens*, *C.botulinum* and *Actinomyces*.
- Gram negative cocci - *N.meningitidis*, *N.gonorrhoeae*.
- Spirochetes - *T.pallidum*, *Leptospira spp.* *B.burgdorferi*.
70. **Tetracyclines.**

Tetracyclines consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity. They include: **tetracycline, doxycycline and minocycline.**

**Mechanism of action.**

Tetracyclines are broad-spectrum bacteriostatic antibiotics. They enter susceptible organisms via passive diffusion and also by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Tetracyclines concentrate intracellularly in susceptible organisms. The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis.

**Antibacterial spectrum.**

The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species. They are commonly used in the treatment of acne and Chlamydia infections (doxycycline), Mycoplasma spp. and Rickettsia.

**Antibacterial resistance.**

Three mechanisms of resistance to tetracycline and its analogues have been described:

1. impaired influx or increased efflux by an active transport protein pump;
2. ribosome protection due to production of proteins that interfere with tetracycline binding to the ribosome; and
3. enzymatic inactivation.

The most important of these are production of an efflux pump and ribosomal protection. Tet(AE) efflux pump-expressing gram-negative species are resistant to the older tetracyclines, doxycycline, and minocycline.

**Pharmacokinetics.**

**Absorption:**

- Tetracyclines are adequately absorbed after oral ingestion. Administration with dairy products or other substances that contain divalent and trivalent cations decreases absorption, particularly for tetracycline, due to the formation of nonabsorbable chelates. Both doxycycline and minocycline are available as oral and intravenous (IV) preparations.

**Distribution:**

- The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification or to tumors that have a high calcium content. Penetration into most body fluids is adequate. Only minocycline and doxycycline achieve therapeutic levels in the cerebrospinal fluid (CSF).
containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents.

**Distribution:** The fluoroquinolones distribute well into all tissues and body fluids, which is one of their major clinical advantages. Levels are high in bone, urine (except moxifloxacin), kidney, and prostatic tissue, and concentrations in the lungs exceed those in serum. Penetration into cerebrospinal fluid is relatively low except for ofloxacin. Fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus having activity against intracellular organisms.

**Elimination:** Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction.

**Adverse drug reactions.**

- Fluoroquinolones are generally well tolerated. The most common effects are nausea, vomiting, and diarrhea.
- Occasionally, headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop.
- Allergic reactions.
- Convulsions
- Sparfloxacin and moxifloxacin (prolong QT interval) - not to be used in those who are predisposed with arrhythmia or with antiarrhythmics.
- Phototoxicity
- Hepatotoxicity. Trovafloxacin causes serious liver injury and should only be used for life-threatening infections. Therapy should not be longer than 2 weeks.
- Connective tissue problems - they are contraindicated in pregnancy, in nursing mothers, and in children under the age of 18. Articular cartilage erosion occurs in immature experimental animals. In adults, they can infrequently cause ruptured tendons.
- Quinolones are potent enzyme inhibitors and impair the metabolic inactivation of other drugs as warfarin, theophylline and sulphonylureas thus increasing their effects.

**Ciprofloxacin.**

- Used against many systemic infections (except by MRSA, enterococci and pneumococci).
- Useful in treating infections caused by many Enterobacteriaceae and other gram negative bacilli e.g., travellers diarrhoea caused by E.coli.
- Drug of choice for prophylaxis and treatment of anthrax.
- Most potent of the fluoroquinolones for P.aeruginosa infections.
- Alternative to more toxic drugs.
- May act synergistically with β lactams.
- Also of benefit in treating resistant tuberculosis.

**Ofloxacin.**
- For respiratory and urinary tract infections and gonorrhea.

**Norfloxacin.**
- Not effective in systemic infections.
- More potent than nalidixic acid, effective against both gram negative and gram positive organisms.
- Complicated and uncomplicated UTIs and prostatitis.

**Levofloxacin**
- Isomer of ofloxacin.
- Primarily used in the treatment of prostatitis. Due to E.coli and of STDs except syphilis.
- Alternative therapy option in patients with gonorrhea.
- Very good activity against respiratory infections due to S.pneumoniae.

**Gatifloxacin.**
- Very good activity against respiratory infections due to S.pneumoniae.

**Moxifloxacin.**
- Enhanced activity against gram positive organisms (e.g. S.pneumoniae) and also against anaerobes (e.g. B.fragilis).
- Very poor activity against P.aeruginosa.

**Trovafloxacin.**
- Combined with aminoglycosides in P.aeruginosa infections.
- Severe hepatotoxicity therefore should be restricted to life-threatening infections.

*Fluoroquinolones should be avoided during pregnancy, nursing mothers and children because they damage growing bone and cartilage.*
Atropine is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. Diazepam is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.
The therapeutic use of scopolamine is limited to prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days.

**Ipratropium and tiotropium.**

They are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Ipratropium is also used in the acute management of bronchospasm in asthma. Both agents are delivered via inhalation. Because of their positive charges, these drugs do not enter the systemic circulation or the CNS, isolating their effects to the pulmonary system.

**Benztropine and trihexyphenidyl.**

They are useful as adjuncts with other antiparkinsonian agents to treat Parkinson's disease and other types of parkinsonian syndromes, including antipsychotic induced extrapyramidal symptoms.
Organ system effects.

**CNS** - undesirable feelings such as nervousness to an extent of feeling disastrous. Noncatecholamines with indirect actions, which easily enter the CNS from the circulation produce from mild alerting to elevation of the mood, insomnia, euphoria anorexia; psychotic behaviour at the highest level.

**Eye** - mydriasis. Alpha agonists increase the outflow of aqueous humor from the eye. Beta antagonists decrease the production of aqueous humor.

**Blood vessels** - alpha 1 receptors increase arterial resistance. Beta 2 receptors promote smooth muscle relaxation. The skin and splanchnic vessels have alpha 1 receptors and constrict in the presence of norepinephrine. Vessels in skeletal muscle dilate on beta receptor activation.

**Cardiovascular system** - beta 1 receptors increase cAMP and calcium influx also increases in cardiac cells. Pacemaker activity increases. Conduction velocity in AV node increases. Contractility increases.

**Blood pressure** - phenylephrine increases peripheral arterial resistance and decrease venous capacitance thus increases blood pressure. The rise of blood pressure elicits a baroreceptor-mediated increase in vagal tone which slowing heart rate. Isoproterenol decreases peripheral resistance by dilating certain vascular beds, but increases cardiac output.

**Respiratory tract** - beta 2 receptors that cause relaxation. The blood vessels of the upper respiratory tract mucosa contain alpha 1 receptors; the decongestant action of adrenoceptor stimulants is clinically useful.

**GI tract** - relaxation of gastrointestinal muscles.

**Genitourinary tract** - uterus contains alpha and beta receptors. Beta 2 receptor activation mediates relaxation. The specific subtype of alpha 1 receptors in the bladder base, urethral sphincter, mediate contraction and therefore promote urinary retention. Beta 2 receptors of the bladder wall mediate relaxation.

**Exocrine glands** - the saliva is dense after adrenoceptor stimulation. The apocrine sweat glands, located on the palms, associated with psychologic stress respond to stimulation with increased sweat production.
**Metabolic effects** - activation of beta adrenoceptors in fat cells leads to increased lipolysis. Enhances glycogenolysis in the liver thus increased glucose is released into circulation. Epinephrine or other mimetic drugs promote the uptake of potassium into cells, a fall in extracellular potassium. Insulin secretion is stimulated by beta receptors and inhibited by alpha 2 receptors. Similarly, renin secretion is stimulated by beta 1 receptors and inhibited by alpha 2 receptors.

**Adrenergic agonists.**

**Direct acting agonists** - act directly on alpha or beta receptors, effects similar to those following stimulation of sympathetic nerves of epinephrine release.
- Epinephrine
- Norepinephrine
- Isoproterenol
- Phenylephrine

**Indirect acting agonists** - causes the release of norepinephrine from the cytoplasm or vesicles of the adrenergic neuron. NE then stimulates the alpha or beta receptors.
- Amphetamine
- Tyramine

**Mixed action agonists** - directly stimulate adrenoceptors and cause the release of NE from the adrenergic neuron.
- Ephedrine
- Metaraminol

**Direct acting adrenomimetics.**

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

**Catecholamines.**

**Epinephrine.**

Epinephrine is one of the four catecholamines (epinephrine, norepinephrine, dopamine, and dobutamine) commonly used in therapy. Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

**Therapeutic uses.**

**Bronchospasm:** Epinephrine is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. Thus, in treatment of acute asthma and anaphylactic shock, epinephrine is the
Norepinephrine is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure.

**Pharmacokinetics.**

Norepinephrine is given IV for rapid onset of action. The duration of action is 1 to 2 minutes, following the end of the infusion. It is rapidly metabolized by MAO and COMT, and inactive metabolites are excreted in the urine.

**Adverse effects.**

Norepinephrine is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein. If extravasation (leakage of drug from the vessel into tissues surrounding the injection site) occurs, it can cause tissue necrosis. It should not be administered in peripheral veins, if possible. Impaired circulation from norepinephrine may be treated with the α receptor antagonist phentolamine.

**Dopamine.**

The immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. Dopamine can activate α- and β-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors. In addition, D1 and D2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur on peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

**Actions.**

**Cardiovascular:** Dopamine exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects. At very high doses, dopamine activates α1 receptors on the vasculature, resulting in vasoconstriction.

**Renal and visceral:** Dopamine dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera. Dopamine is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

**Therapeutic uses.**

Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase
32. Beta adrenomimetics (beta agonists).

**Isoproterenol.**

It is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its non-selectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output. It is as active as epinephrine in this action. Isoproterenol also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressures. Isoproterenol is a potent bronchodilator (β2 effect). Therapeutic uses include bronchodilator in asthma, and stimulator of the heart. They are given sublingually, parenterally or as an inhaled aerosol.

**Dobutamine.**

It is a synthetic, direct-acting catecholamine that is a β1 receptor agonist. It increases cardiac rate and output with few vascular effects. Dobutamine is used to increase cardiac output in acute heart failure, as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs. Dobutamine should be used with caution in atrial fibrillation, because it increases AV conduction.

**Albuterol and terbutaline.**

Albuterol and terbutaline are short-acting β2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler. Albuterol is the short-acting β2 agonist of choice for the management of acute asthma symptoms. Terbutaline is also used as a uterine relaxant to suppress premature labor and as a bronchodilator. Terbutaline has a longer duration of action. One of the most common side effects of these agents is tremor. Other side effects include restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β1 receptor activation), especially in patients with underlying cardiac disease.

**Salmeterol and formoterol.**

Salmeterol and formoterol are long acting β agonists that are β2 selective. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol. Unlike formoterol, salmeterol has a somewhat delayed onset of action. Salmeterol and formoterol
**Effects on the Cardiovascular System** - Beta-blocking drugs given chronically lower blood pressure in patients with hypertension. The mechanisms probably include suppression of renin release and effects in the central nervous system. Beta-receptor antagonists have prominent effects on the heart and are very valuable in the treatment of **angina** and **chronic heart failure** and following **myocardial infarction**. The **negative inotropic and chronotropic effects** reflect the role of adrenoceptors in regulating these functions. Slowed atrioventricular conduction with an increased PR interval is a related result of adrenoceptor blockade in the atrioventricular node.

**Effects on the Respiratory Tract** - Blockade of the $\beta_2$ receptors in bronchial smooth muscle may lead to an increase in airway resistance, particularly in patients with asthma. Beta 1 receptor antagonists such as metoprolol and atenolol may have some advantage over nonselective $\beta$ antagonists when blockade of $\beta_1$ receptors in the heart is desired and $\beta_2$ receptor blockade is undesirable.

**Effects on the Eye** - Beta-blocking agents reduce intraocular pressure, especially in glaucoma. The mechanism usually reported is decreased aqueous humor production.

**Metabolic and Endocrine Effects** - Beta-receptor antagonists such as propranolol inhibit sympathetic nervous system stimulation of lipolysis. Beta 1-receptor selective drugs may be less prone to inhibit recovery from hypoglycemia. Beta 1-receptor antagonists are much safer in those type 2 diabetic patients who do not have hypoglycemic episodes. The chronic use of $\beta$-adrenoceptor antagonists has been associated with increased plasma concentrations of very-low-density lipoproteins (VLDL) and decreased concentrations of HDL cholesterol. These changes are potentially unfavorable in terms of risk of cardiovascular disease.

**Specific agents.**

**Propranolol** is a nonselective $\beta$ antagonist and the prototypical $\beta$-blocking drug. It has low and dose-dependent bioavailability. A long-acting form of propranolol is available; prolonged absorption of the drug may occur during a 24-hour period.

**Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol** members of the $\beta_1$-selective group. These agents may be safer in patients who experience bronchoconstriction in response to propranolol. Beta 1 selective antagonists may be preferable in patients with diabetes or peripheral vascular disease when therapy with a $\beta$ blocker is required, since $\beta_2$ receptors are probably important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

**Nebivolol** is the most highly selective $\beta_1$ adrenergic receptor blocker, though some of its metabolites do not have this level of specificity. Nebivolol has the additional quality of eliciting vasodilation. This is due to an action of the drug on endothelial nitric oxide.
44. Antiepileptic drugs.

Epilepsy is a common chronic neurological disorder characterised with occurrence of recurrent seizures. Seizures are transient brain dysfunctions induced by episodic high frequency discharge of impulses by a group of neurons in the brain. Epilepsy can be seen as a family of brain disorders sharing a common manifestation by seizures.

Classification of seizures:

- **Partial (focal) seizures**
  - Simple partial seizures
  - Complex partial seizures
- **Generalised seizures**
  - Generalised tonic clonic (grand mal) seizures
  - Absence seizures (petit mal)
  - Tonic seizures
  - Atonic seizures
  - Clonic and myoclonic seizures
  - Infantile spasms

**Focal seizures.**

Focal seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Focal seizures may progress to become generalized tonic–clonic seizures.

- **Simple partial:** These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity and are confined to a single locus in the brain. It lasts for up to 60 seconds. The electrical discharge does not spread, and the patient does not lose consciousness or awareness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. Simple partial seizures may occur at any age.

- **Complex partial:** These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Confused behaviour, unnecessary movements and emotional changes lasting from 30 seconds up to 2 minutes. Complex partial seizures may occur at any age.

**Generalized seizures.**
**Opioid competitive antagonists.**

Naloxone ฿, κ and δ antagonist - short duration of action.  
Naltrexone ฿, κ and δ antagonist - duration of action for about 72 hours.  
Nalorphine ฿ antagonist/ κ agonist.  

Low efficacy for mild and moderate pain.  
- Codeine  
- Dihydrocodeine  
- Dextropropoxyphene  
- Oxycodone  
- Pentazocine  
- Tramadol  

High efficacy for severe pain.  
- Morphine  
- Fentanyl  
- Alfentanil  
- Sufentanyl  
- Buprenorphine  
- Heroin  
- Methadone  
- Pethidine  

Analgesics in chronic tumour pain according to WHO:  
- 1st step (weak pain) - paracetamol or NSAIDS.  
- 2nd step (moderate pain) - weak opioids e.g. codeine, dihydrocodeine, oxycodone.  
- paracetamol or NSAIDS.  
- 3rd step (severe pain) - strong opioids e.g. fentanyl, morphine.  
- Paracetamol or NSAIDS.  

**Opioid antagonists which doesn’t cross BBB.**  

Loperamide and racecadotril stimulate ฿ and δ receptors, present in the small and large intestines. Activation of ฿ receptors decreases peristaltic movements. Activation of δ receptors contributes to their antisecretory effects. Loperamide directly stimulates ฿ and δ receptors.  
Racecadotril blocks enzyme enkephalinase and increases local concentration of enkephalins in intestinal mucosa which then stimulate ฿ and δ receptors. This drug can be used orally for children under the age of 5 but loperamide is contraindicated in children younger than 5 years of age.  

**Opioid intoxication.**  

Symptoms of intoxication can include:
Sedation can be defined as a suppression of responsiveness to a constant level of stimulation, with decreased spontaneous activity and ideation. A hypnotic drug should produce encourage the onset and maintenance of state or sleep that as far as possible resembles the natural state of sleep. Hypnotic effects involve more pronounced depression of the CNS than sedation, and this can be achieved with most sedative drugs simply by increasing the dose.

In anxiety states the fear response occurring in an anticipatory manner independently of external events. Anxiety is an unpleasant state of inner instability often accompanied by nervous behaviour, such as pacing back and forth, somatic complaints and rumination.

An effective anxiolytic agent should reduce anxiety and exert a calming effect with little or no effect on motor and mental function. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes referred to as anxiolytic or minor tranquilizers). Because many of the antianxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic agents. In addition, some have anticonvulsant activity. Graded dose dependent depression of the CNS function is characteristic of sedative-hypnotic drugs.

Anxiety disorders include:
- Generalized anxiety disorder (an ongoing state of excessive anxiety lacking any clear reason).
- Panic disorder (attacks of overwhelming fear occurring in association with somatic symptoms e.g. sweating, tachycardia, chest pain etc.).
- Phobias (strong fears of specific things or situations e.g. snakes, flying).
- Posttraumatic stress disorder (anxiety triggered by insistent recall of past stressful experiences).

Sleep cycle.

There are two forms of sleep: REM (rapid eye movement) sleep and non-REM sleep. REM is associated with dreaming. It accounts for 25% of normal sleep, coming in longer periods towards morning. The rest of our sleep is spent in NREM, which consists of four stages from light sleep (stage 1) to deep sleep (stage 4).

Classification of hypnotics.
neuronal inhibition. Like benzodiazepines, the actions of zolpidem are antagonised by flumazenil. They have minimal anticonvulsant and muscle relaxant effects. The risk of development of tolerance and dependance with extended use is less than with the use of hypnotic BZs. They are rapidly metabolised to inactive metabolites by the liver, has half life of 1½ to 3 ½ hours. Dosage reduction must be done in elderly with hepatic dysfunction.

**Zopiclone & Imovane.**
A cyclopyrrolole in structure. It has a fairly fast onset of action which last for 6 - 8 hours, making it an effective drug both for initial and maintenance of insomnia. Its’s duration of action is prolonged in the elderly.

**Zaleplon** resembles zolpidem, has half life of 1 hour. It has rapid onset and short duration of action, they are favourable properties for those patients who have difficulty falling asleep.

**Barbiturates.**

**Mechanism of action.**
The sedative–hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAergic transmission. The binding site on barbiturates on the GABA receptor is distinct from that of the benzodiazepine. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors. Anesthetic concentrations of pentobarbital also block high-frequency sodium channels. All of these molecular actions result in decreased neuronal activity.

**Therapeutic uses.**

**Anesthesia:** The ultra–short-acting barbiturates, such as thiopental, have been used intravenously to induce anesthesia but have largely been replaced by other agents.

**Anticonvulsant:** Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression. It is used in long-term management of tonic–clonic seizures. Phenobarbital may be used for the treatment of refractory status epilepticus.

**Sedative/hypnotic:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages.

**Pharmacokinetics.**
Barbiturates are well absorbed after oral administration and distribute throughout the body. All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue. This movement is important in causing the short duration of action of thiopental and similar short-acting derivatives. Barbiturates readily cross the placenta and can depress the fetus. These agents are metabolized in the liver, and inactive metabolites are excreted in urine.
Adverse effects.
Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness. Hypnotic doses of barbiturates produce a drug “hangover” that may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur. Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system. Barbiturates are contraindicated in patients with acute intermittent porphyria.
Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death. Death may also result from overdose. Severe depression of respiration is coupled with central cardiovascular depression and results in a shock-like condition with shallow, infrequent breathing. Treatment includes supportive care and gastric decontamination for recent ingestions.

Anxiolytic drugs.
- Benzodiazepines
- Azapirones
- Benzoaxazines
- Sedative H₁ blocker
- Non selective beta blockers
- SSRIs

Buspirone has anxiolytic effects which take days or weeks to develop. It is the most distinctive drug in terms of antianxiety actions, since these are achieved with minimal effects on psychomotor functions. It is not a CNS depressant. It is a partial agonist of dopaminergic and serotoninergic receptors. It only has anxiolytic properties. They have no adverse effects other than dizziness, nausea and headache.

Non selective beta blockers.
Many symptoms of anxiety are due to sympathetic overactivity and these symptoms reinforce anxiety. Propranolol and other non selective beta blockers cut the vicious cycle and provide the symptomatic relief. They do not affect psychological symptoms, such as fear, tension and worry, but are valuable in acutely stressful situations.

Selective serotonin reuptake inhibitors. (SSRIs).
They are effective in obsessive compulsive disorder (OCD), phobias, panic and many types of severe generalised anxiety disorders.